REMARKS

Status of the Claims

Claims 1-5, 10-22, 25-28, 30-34, 44-48 and 62-65 are pending. Claims 25-28, 30-34, 44-48 and 64-65 are withdrawn. Claims 1-5, 10-22, and 62-63 are rejected. Claims 1-5 and 19 were previously amended. Claims 21-22 and 62-63 are amended herein. No new matter is added to the amended claims.

Claim Amendments

Claim 1 is amended to overcome the 35 U.S.C §102 rejection. Amended claim 1 only encompasses covalently reactive ligand analogues (CAL) that comprise a linker at Y''. This amendment is supported by the instant specification, specifically page 34, line 5-page 35, line 16; page 48, line 15-page 49, line 7 and page 74, lines 5-20.

Claims 21-22 are amended to overcome the 35 U.S.C. §112 rejection. Amended claims 21-22 recites the CAL of claim 1 in which the ligand determinant ...[L_1 . . . L_x . . . L_m]... is a polyamino acid. This amendment is supported by the instant specification, specifically page 4, lines 6-22; page 8, lines 17-27; Figure 18; and Example I on page 32, line1- page 56, line 7.

Claims 62 and 63 are amended to overcome the 35 U.S.C. §112 rejection. Amended claim 62 recites the CAL of Claim 1 wherein L_1, L_x and L_m are individual components of the ligand determinant composed of an amino acid residue, sugar residue, a lipid residue or a nucleotide. This amendment is supported by the instant specification, specifically, page 2, lines 6-18; page 10, line 27-page 12, line 2; Examples I-II on page page 32, line1- page 56, line 7. Amino-acid based CALs are described on page 4, lines 6-22; page 8, lines 17-27; and Figures 18, 22. Preparation of DNA-CALs is described on page 10, line 27-page 12, line 2. Additionally, Fig 17A teaches a schematic drawing of overall structure of a large dsDNA-CAL; Fig 17B depicts the chemical structure of a dsDNA-CAL portion where a covalently reactive electrophic groups is attached; and Fig 17C teaches two structures of oligonucleotide-CALs (oligo-CALs), containing different electrophilic group Y.

Amended claim 63 restricts the CAL of claim 62 such that L_1, L_x and L_m are individual components of the ligand determinant composed of an amino acid residue. This amendment is supported by the instant specification, specifically page 4, lines 6-22; page 8, lines 17-27; and Figures 18, 22.

Specification:

On page 3 of the Office Action, the Examiner objects to the specification because references and footnotes are placed periodically throughout. The Examiner suggests that the references be placed at the end of the specification and the footnotes be inserted within the body of the text.

The specification is amended so that references are placed at the end of the specification. Additionally, the footnotes are inserted within the body of the text. Accordingly, Applicants request the withdrawal of the objection to the specification.

The 35 U.S.C. §112 Rejections

Claims 21, 22, 62 and 63 are rejected under 35 U.S.C. §112, first paragraph as failing to meet the written description requirement. Applicant traverses this rejection.

On page 4 of the Office Action, the Examiner states that claims 21, 22, 62 and 63 contain subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor, at the time the application was filed, had possession of the claimed invention. The Examiner states that claims 21 and 22 have redefined that the ligand determinant "is a polypeptide comprising" where previously it was either a linear or non-linear polyamino acid. The Examiner argues that there is no explicit, implicit or inherent support for this change in concept and scope of the claimed invention. The Examiner further argues that the scope of claims 62-63 are not supported by implicit, inherent or explicit support. The Examiner states that in both cases, the claims and specification provide no definition for L1 and Lm, and thus one cannot conclude that they are peptides, polysaccharides, etc. The Examiner argues that given the absence of a definition, one cannot find support that the "ligand determinant" would be a polypeptide comprising a linear or non-linear polyamino acid.

Claims 21, 22, 62 and 63 are amended as described supra. Amended claims 21-22 recite a CAL wherein the ligand determinant is a polyamino acid. This amendment is supported by the instant specification on page 4, lines 6-22; page 8, lines 17-27; and page 32, line1- page 56, line 7. Specifically, Example I teaches CAL IV, which is a CAL derived from the ligand cxEGFR. The Structure of CAL IV is as shown in Fig 1C described on page 4, lines 6-22. Specific covalent binding of CAL IV to four exEGFR-specific NuRs (polyclonal anti-exEGFR IgG, monoclonal antibodies C225, H11 and 111.6) is described in Example I. Additionally, Example 2 in the instant specification teaches specific covalent binding and inactivation of proteolytic anti-VIP antibodies by VIP-CAL. Applicants submit that the specification supports linear and non-linear polyamino acid ligand determinants. Accordingly, Applicants submit that the specification provides adequate guidance for one of skill in the art to make and utilize the CALs encompassed by claims 21-22.

Amended claim 62 recites the CAL of Claim 1 wherein L_1, L_x and L_m are individual components of the ligand determinant composed of an amino acid residue, sugar residue, a lipid residue or a nucleotide. This amendment is supported by the instant specification as described supra. Specifically, amino-acid based CALs are described on page 4, lines 6-22; page 8, lines 17-27; and Figures 18, 22. DNA-CALs are

described on page 10, line 27-page 12, line 2. Though structure drawings of lipid- and carbohydrate-based CALs are not shown in the specification, Applicants submit that the design of such CALs can be readily predicted from the art, based on the instant invention. For instance, lipid receptor ligands such as N-arachidonoylethanolamine, a cannabinoid receptor agonist; and sugar receptor ligands such as carbohydrate units of oligomannose or hybrid type of human cell surface glycoproteins recognized by bacterial lectins. Accordingly, Applicants submit that the specification provides adequate guidance for one of skill in the art to make and utilize the CALs encompassed by claim 62.

Amended claim 63 is dependent on claim 62 and restricts the CAL of claim 62 such that L_l, L_x and L_m are individual components of the ligand determinant composed of an amino acid residue. As described supra, this is supported by the instant specification, specifically page 4, lines 6-22; page 8, lines 17-27; and Figures 18, 22. Applicants submit that the specification provides adequate guidance for one of skill in the art to make and utilize the CALs encompassed by claim 63.

Based on the above remarks, Applicants respectfully request the withdrawal of the rejection of claims 21-22 and 62-63 under 35 U.S.C. §112, first paragraph.

Claims 1-5, 10-22, 62 and 63 are rejected under 35 U.S.C. §112, first paragraph as failing to comply with the written description requirement. Applicants respectfully traverse this rejection.

On page 5 of the Office Action, the Examiner states that claims 1-5, 10-22, 62 and 63 contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed. The Examiner states that the Applicants have provided few compounds (Fig. 18) which are within the scope of the claimed invention, additionally, these compounds are closely related in structure. The Examiner argues that besides these closely related compounds, there is no description of compounds which are within the metes and bounds of the claims that would function as claimed-a covalently active ligand analog. The Examiner argues that claims 1-5, 10-22, 62 and 63 are incomplete because these claims omit essential elements L1, and Lm. The Examiner states that the group of elements "...L1...Lx...Lm..." are stated in the claims as "components defining a ligand determinant", where Lx is defined in a dependent claim as an amino acids, however, L1 and Lm are not defined. Additionally, the Examiner states that "a ligand determinant" is not defined, and it is also unclear what "a component of a ligand determinant" is.

Claim 1 and dependent claims are drawn to covalently reactive ligand analogues (CAL). This amendment is supported by the instant specification, specifically, amino-acid based CALs are described on page 4, lines 6-22; page 8, lines 17-27; and Figures 18, 22. DNA-CALs are described on page

10, linc 27-page 12, line 2. Example I teaches CAL IV, which is a CAL derived from the ligand exEGFR. Example II teaches specific covalent binding and inactivation of proteolytic anti-VIP antibodies by VIP-CAL which is a CAL derived from the ligand VIP. Additionally, two CALs for specific covalent targeting of anti-FVIII found in hemophilia patients under FVIII treatment are described in Example IV. Applicants submit that the CALs of Fig. 18 recited by the Examiner on page 5 of the instant Office Action, form only a small part of the CAL examples encompassed by the specification. The CALs of Fig. 18 are closely related in structure because these CALs target the same NuR. Applicants submit that as described supra, the instant invention encompasses many diverse CALs targeting diverse NuRs, which is supported by the instant specification.

Applicants further submit that the term 'Ligand determinant' is the L moiety, which is defined on page 19, line 9 of the instant specification as a ligand structure unit that provides weak bonding interactions. Components of a ligand determinant are defined on page 19, line 26-page 20, line 6 of the instant specification. Specifically, the specification teaches that when the ligand determinant (L) is a polypeptide, the components of a ligand determinant (i.e. L_1, L_x, L_m) are the component amino acids of the ligand determinant recognized weakly by the NuR. When the ligand determinant (L) is an oligonucleotide, oligosaccharide or an oligolipidic repeat structure, the components of a ligand determinant (L_1, L_x, L_m) are the component nucleotides, saccharides, and lipids. The specification also teaches that when the ligand determinant (L) is a polypeptide, the components of a ligand determinant ($L_1 \ldots L_x \ldots L_m$) can be a linear or discontinuous set of amino acids that are spatially in proximity with electrophile (E). Accordingly, based on these arguments, Applicants submit that the terms 'ligand determinant', 'a component of a ligand determinant', L1 and Lm are all supported by the instant specification. The specification also provides ample guidance for one of skill in the art to design and arrive at the compounds encompassed by claim 1 and dependent claims.

Based on the above remarks, Applicants respectfully request the withdrawal of the rejection of claims 1-5, 10-22, 62 and 63 under 35 U.S.C. §112, first paragraph.

The 35 U.S.C. §102 Rejections

Claims 1-5, 13, 18, 19, 21, 22, 62 and 63 are rejected under 35 U.S.C. §102(e) as being anticipated by **Tanaka** (U.S. Patent No. 5,434,133). Applicants respectfully traverse this rejection.

On page 7 of the Office Action, the Examiner states that **Tanaka** teaches a compound comprising a peptide portion with Ser-Gly-Leu-Gly which broadly reads upon the functionalities Y'', Y' and Y, with the Cys of the A-B moiety being the 'functional group' of L' and L_x, and the remainder of the compound satisfying the requirements of the 'ligand determinant'. Based on this reasoning, the Examiner concludes that **Tanaka** anticipates claims 1-5, 13, 18, 19, 21, 22, 62 and 63.

Applicants submit that **Tanaka** teaches a single peptide molecule that has been cyclized by means of a disulfide bonded of the general formula: (A)-(B)-(C)-Gly-(D)-(E)-(F)-Asp-Arg-Ile-Gly-(G)-(H)-Ser-Gly-Leu-Gly-(B)-(I), wherein: (A) represents H-, H-Gly, H-Lys-Gly, H-Ser-Lys-Gly, H-Leu-Ser-Lys-Gly, H-Gly-Leu-Ser-Lys-Gly, H-Ser, H-Ser-Ser, H-Arg-Ser-Ser, H-Arg-Arg-Ser-Ser, H-Leu-Arg-Arg-Ser-Ser, H-Ser-Leu-Arg-Arg-Ser-Ser; (B) represents H-Cys or Pmp; (C) represents Phe-, pCl-Phe, pF-Phe, pNO2-Phe or Cha; (D) represents Ile, Val, Aib, tLeu, Gly or Leu; (E) represents Lys or Arg; (F) represents Ile, Leu or Met; (G) represents Ser or Ala; (H) represents Met or Gln; (I) represents -OH, -Asn-OH, -Asn-Ser-OH, -Asn-Ser-Phe-OH, -Asn-Ser-Phe-Arg-OH or -Asn-Ser-Phe-Arg-Tyr-OH; and the two (B)s are connected by a disulfide bond.

Applicants submit that the peptides taught by **Tanaka** do not comprise an electrophilic group (Y). As recited in claim 1, the covalently reactive ligand analogue (CAL) of the instant invention essentially comprise a covalently reactive electrophilic group (Y) that reacts specifically with a receptor that binds to said ligand determinant. Thus, the peptide taught by **Tanaka** is not a CAL because it lacks the covalently reactive electrophilic group (Y) which is an essential structural component of CALs. Accordingly, Applicants submit that **Tanaka** does not anticipate the instant invention.

To anticipate amended independent claim 1 and dependent claims **Tanaka** must teach every element recited in the instant claims. Applicants submit that **Tanaka** does not identify the claimed invention. Accordingly, based on these remarks, Applicants respectfully request the withdrawal of the rejection of claim 1 and dependent claims 2-5, 13, 18, 19, 21, 22, 62 and 63 under 35 U.S.C. §102(e).

Claims 1-5, 13, 18, 19, 21, 22, 62 and 63 stand rejected under 35 U.S.C. §102(e) as being anticipated by **Paul** (U.S. Patent No. 6,855,804). Applicants respectfully traverse this rejection.

The Examiner argues that **Paul** teaches the compound of Fig. 4B, which anticipates the instant invention. Amended claim 1 encompasses covalently reactive ligand analogues (CAL) that comprise a ligand determinant comprising a component unit L_x with a functional group-L' that is attached by means of a linker-Y" to Y, which is a covalently reactive electrophilic group that reacts specifically with a receptor that binds to said ligand determinant.

Paul teaches covalently reactive transition state analogs and methods of use thereof. The compound of Fig. 4B cited by the Examiner is the end-product from the reaction of a hapten phosphonate monoester and trypsin followed by tryptic digestion. In this reaction, the starting trypsin molecule serves as the NuR. There is no precedent for a further exchange reaction of this end-product with a different NuR. Applicants submit that this compound is not a covalently reactive ligand analogues (CAL) that comprises a ligand determinant comprising a component unit L_x with a functional group-L' that is attached by means of a

linker-Y" to Y-a covalently reactive electrophilic group that reacts specifically with a receptor that binds to the ligand determinant. Applicants submit that the compound taught by **Paul** does not comprise a linker that attaches the covalently reactive electrophilic group Y to the functional group L'. Paragraphs 218, 360, and 423 of the instant specification teach the importance of linkers of different lengths, in order to allow conformational flexibility that is vital to the utility of CALs. In addition the linker contains a reactive group that facilitates chemical synthesis of CALs. The trypsin end-product compound of **Paul** does not teach or obviate the use of such a vital linker necessary for optimal CAL properties. Based on this, the instant compound taught by **Paul** does not anticipate the CALs of the instant invention. Accordingly, Applicants submit that **Paul** does not teach or anticipate the instant invention.

To anticipate amended independent claim 1 and dependent claims **Paul** must teach every element recited in the instant claims. Based on this, Applicants submit that **Paul** does not identify the claimed invention. Accordingly, based on these remarks, Applicants respectfully request the withdrawal of the rejection of claim 1 and dependent claims 2-5, 13, 18, 19, 21, 22, 62 and 63 under 35 U.S.C. §102(e).

Double Patenting

Claims 1-5, 10-22, 62 and 63 are provisionally rejected on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-66 of copending Application No. 10/581,294. The Examiner argues that the claims are not patentably distinct from each other because the method of 10/581,294 makes the compounds of the instant claims.

Applicants submit a terminal disclaimer under 37 CFR §1.321(c). Accordingly, Applicants request that the provisional nonstatutory double-patenting rejection of claims 1-5, 10-22, 62 and 63 be withdrawn.

Claims 1-5, 10-22, 62 and 63 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-22 of US patent No. 7,524,663. The Examiner argues that the claims are not patentably distinct from each other because the compound used in 7,524,663 anticipate the instant claims.

The compound cited by the Examiner is the end-product from the reaction of a hapten phosphonate monoester and trypsin followed by tryptic digestion. In this reaction, the starting trypsin molecule serves as the NuR. There is no precedent for a further exchange reaction of this end-product with a different NuR. Applicants submit that this compound is not a covalently reactive ligand analogues (CAL) that comprises a ligand determinant comprising a component unit L_x with a functional group-L' that is attached by means of a linker-Y" to Y-a covalently reactive electrophilic group that reacts specifically with a receptor that

binds to the ligand determinant. Applicants submit that the compound taught by USPN 7,524,663 does not comprise a linker that attaches the covalently reactive electrophilic group Y to the functional group L'. Paragraphs 218, 360, and 423 of the instant specification teach the importance of linkers of different lengths, in order to allow conformational flexibility that is vital to the utility of CALs. In addition the linker contains a reactive group that facilitates chemical synthesis of CALs. The trypsin end-product compound of USPN 7,524,663 does not teach the use of the vital linker necessary for optimal CAL properties. Thus, this compound taught by USPN 7,524,663 does not render obvious the CALs of the instant invention. Accordingly, Applicants request that the provisional nonstatutory double-patenting rejection of claims 1-5, 10-22, 62 and 63 in view of USPN 7,524,663 be withdrawn.

Claims 1-5, 10-22, 62 and 63 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-10 of USPN 6,885,804. The Examiner argues that the claims are not patentably distinct from each other because the covalently reactive transition state antigen analogs of USPN 6,885,804 anticipate the instant CAL.

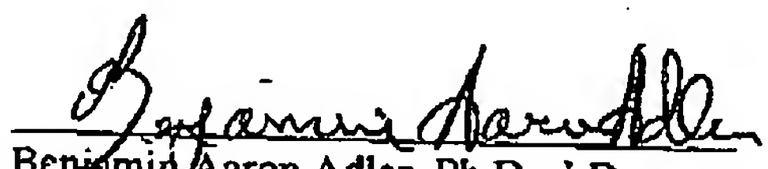
The compound cited by the Examiner is the end-product from the reaction of a hapten phosphonate monoester and trypsin followed by tryptic digestion. In this reaction, the starting trypsin molecule serves as the NuR. There is no precedent for a further exchange reaction of this end-product with a different NuR. Applicants submit that this compound is not a covalently reactive ligand analogues (CAL) that comprises a ligand determinant comprising a component unit L_x with a functional group-L' that is attached by means of a linker-Y" to Y-a covalently reactive electrophilic group that reacts specifically with a receptor that binds to the ligand determinant. Applicants submit that the compound taught by USPN 6,855,804 does not comprise a linker that attaches the covalently reactive electrophilic group Y to the functional group L'. Paragraphs 218, 360, and 423 of the instant specification teach the importance of linkers of different lengths, in order to allow conformational flexibility that is vital to the utility of CALs. In addition the linker contains a reactive group that facilitates chemical synthesis of CALs. The trypsin end-product compound of USPN 6,855,804 does not teach the use of the vital linker necessary for optimal CAL properties. Thus, the compound taught by USPN 6,855,804 does not render obvious the CALs of the instant invention. Accordingly, based on these remarks, Applicants request that the provisional nonstatutory double-patenting rejection of claims 1-5, 10-22, 62 and 63 be withdrawn.

This is intended to be a complete response to the Office Action mailed September 1, 2009. If any issues remain outstanding, please telephone the undersigned attorney of record for immediate resolution. Applicants enclose a Petition for a Three Month Extension of Time. Please charge the $555 extension fee under 37 C.F.R. §1.17(a) and the $70 Fee for one (1) Terminal Disclaimer under 37 C.F.R.

§1.20(d) to the credit card identified on the enclosed Form PTO-2038. **Only in the absence** of Form PTO-2038, please debit any applicable fees from Deposit Account upon which the undersigned is allowed to draw.

Respectfully submitted,

Date: Mar. 1, 2010



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